7-10 novembre 2013, Bari

12° Congresso Nazionale AME
6th Joint Meeting with AACE

Update in Endocrinologia Clinica

TERAPIA DELLA RETINOPATIA DIABETICA: QUANDO E COME

Terapia farmacologica sistemica

Marcella Balbo

SSD Endocrinologia e Malattie Metaboliche

ASO Santi Antonio e Biagio e Cesare Arrigo

Alessandria

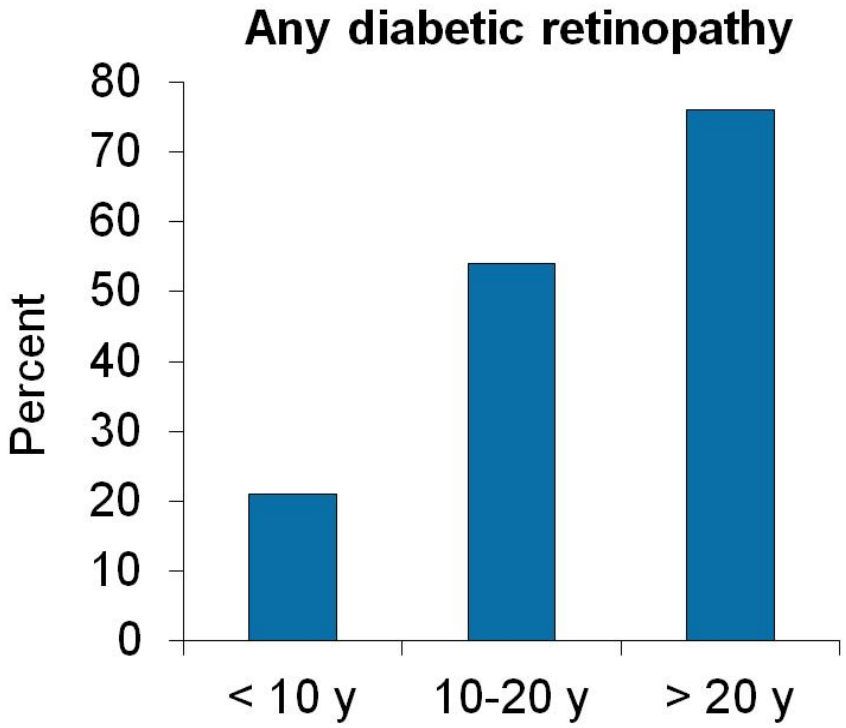
- Ruolo del controllo glicemico
- Ruolo del controllo PAO e del sistema RAA
- Ruolo della terapia anti-lipidica

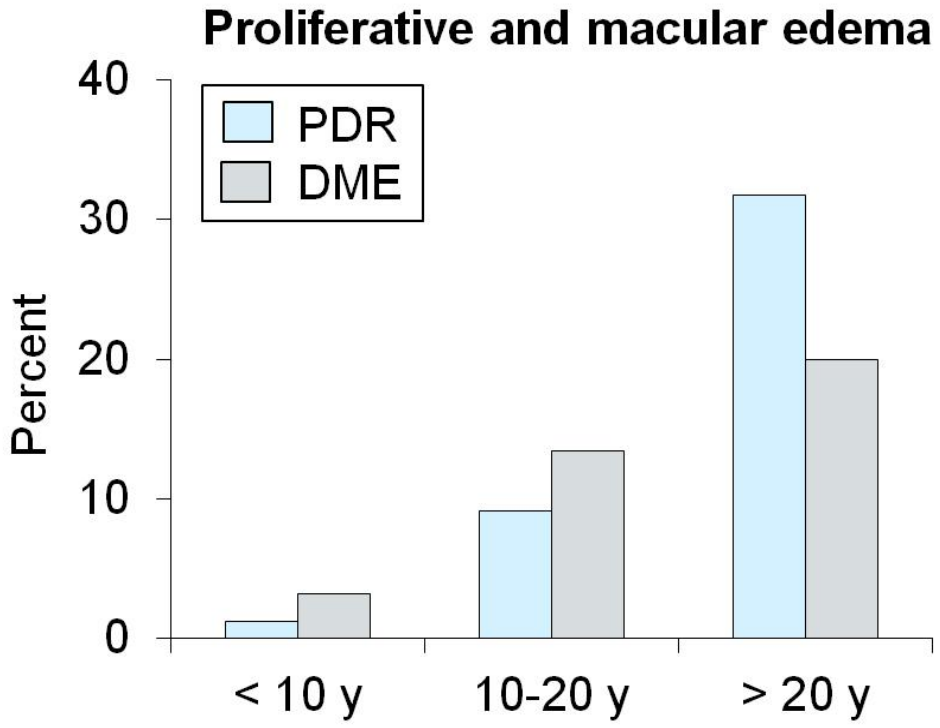
Perche' prevenire e curare la retinopatia diabetica?

- Il diabete mellito è la causa più comune di cecità tra gli individui in età lavorativa (20-65 anni).
- La prevalenza di cecità dovuta a diabete, nei paesi occidentali, è stimata tra 1.6-1.9/100.000
- La presenza di retinopatia diabetica raddoppia il rischio di eventi cardiovascolari nel DM2 e lo quadruplica nel DM1

RD e durata di malattia diabetica

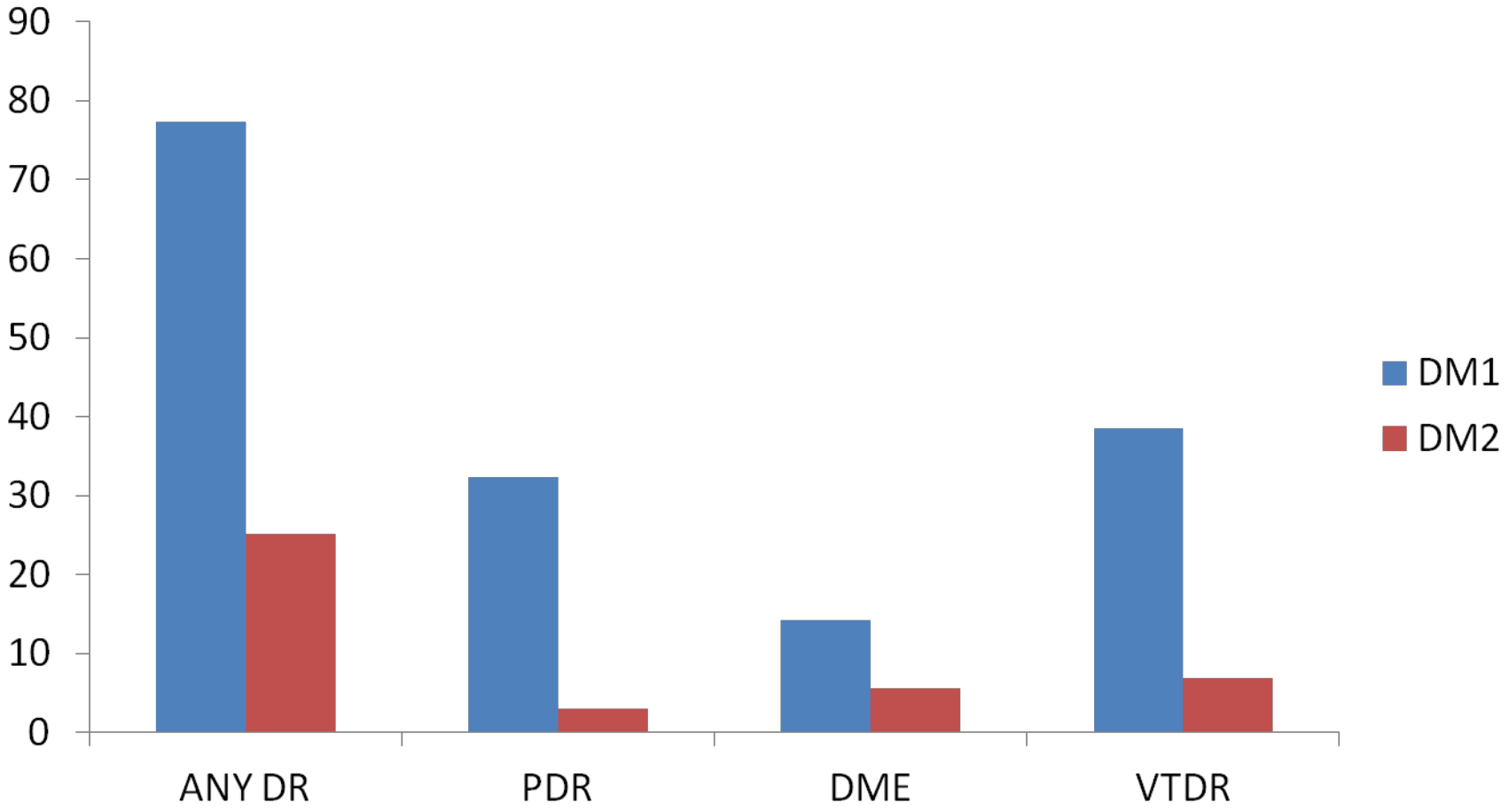
Combined analysis: 35 studies (1980-2008) of 22,896 diabetic persons





Yau JW, et al. *Diabetes Care*. 2012;35:556-564.[46]

Prevalenza di RD in DM1 e DM2



Yau JW et al, Diabetes Care 35:556-564, 2012

RD e HbA1c

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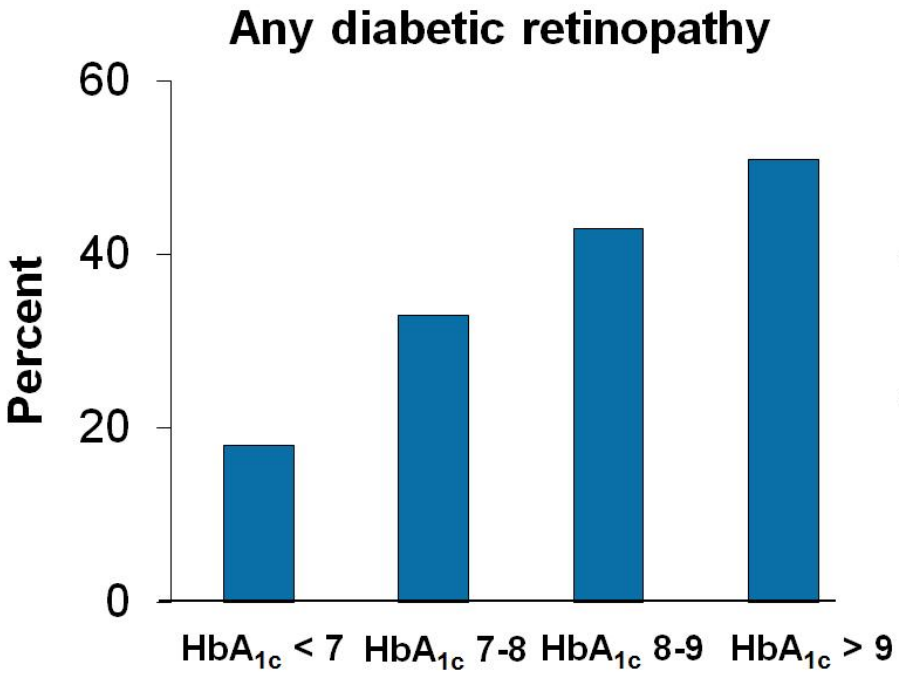
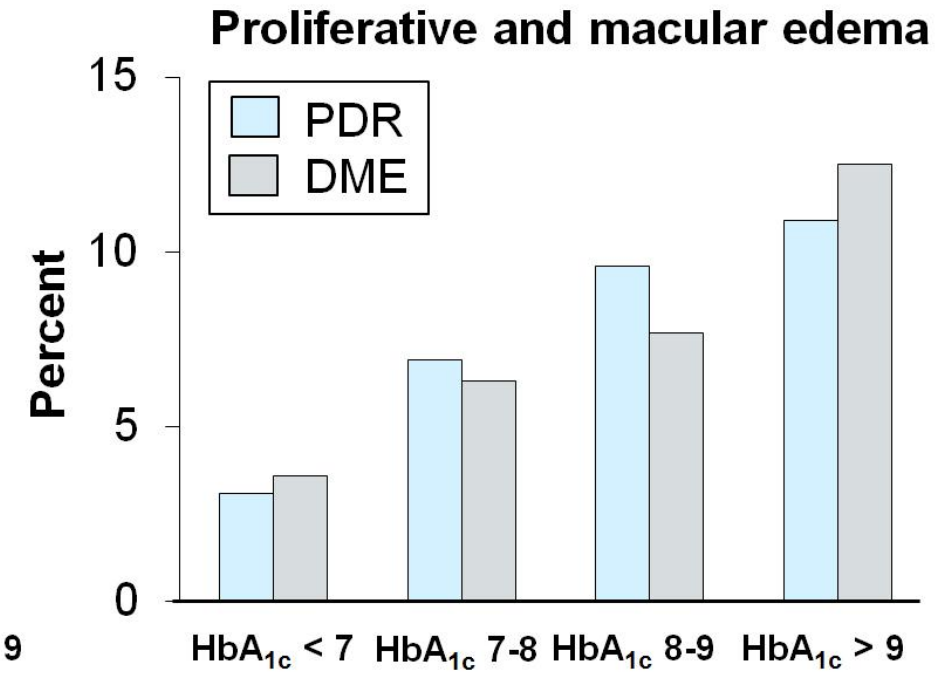




Yau JW, et al. *Diabetes Care*. 2012;35:556-564.[46]

RD e COMPENSO GLICEMICO

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

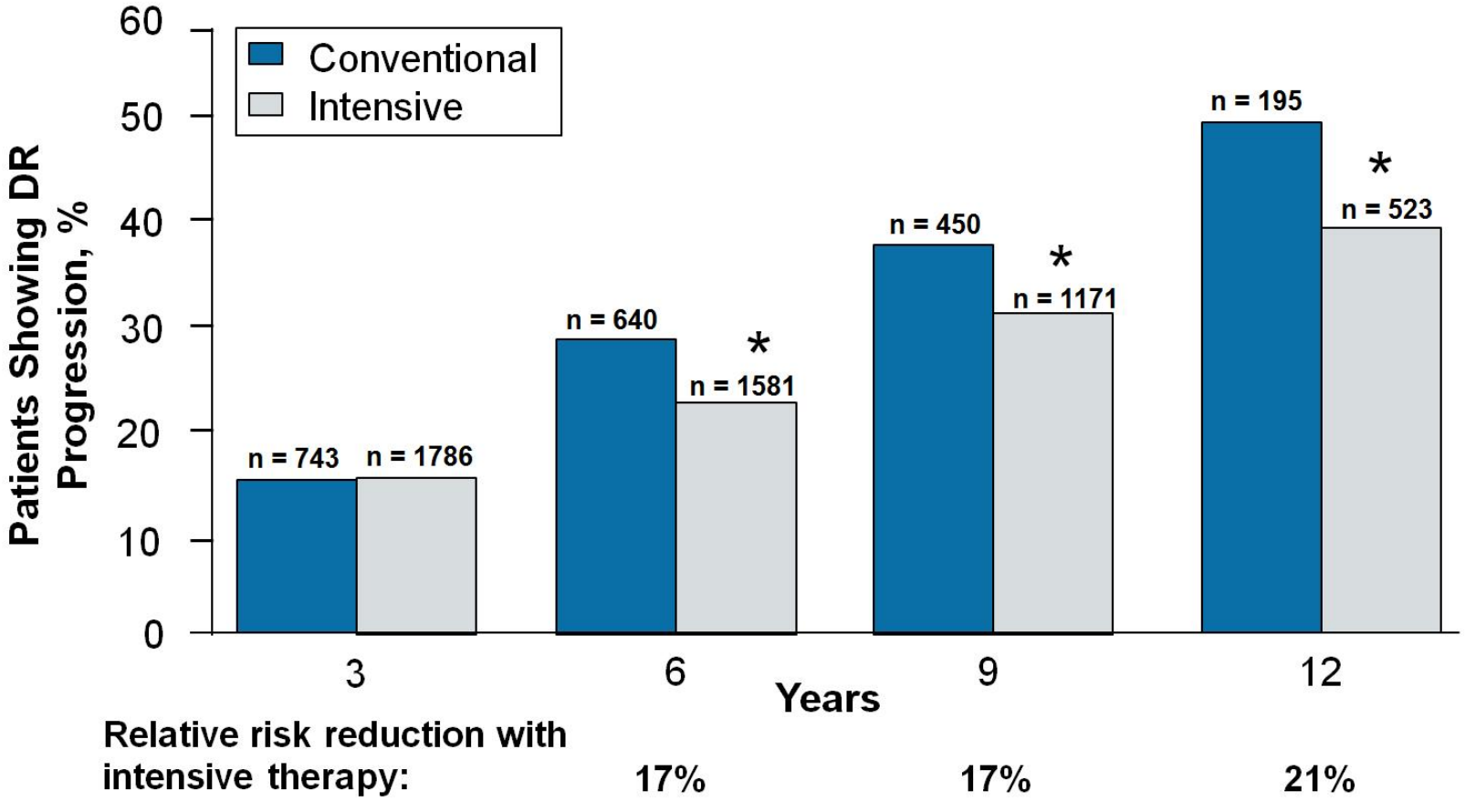
Table 2. Development and Progression of Long-Term Complications of Diabetes in the Study Cohorts and Reduction in Risk with Intensive as Compared with Conventional Therapy.*

COMPLICATIONS	PRIMARY PREVENTION			SECONDARY INTERVENTION			BOTH COHORTS†
	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	CONVENTIONAL THERAPY	INTENSIVE THERAPY	RISK REDUCTION	RISK REDUCTION
	rate/100 patient-yr		*% (95% CI)*	*rate/100 patient-yr*		*% (95% CI)*	*% (95% CI)*
≥3-Step sustained retinopathy.	4.7	1.2	76 (62–85)‡	7.8	3.7	54 (39–66)‡	63 (52–71)‡
Macular edema§	—	—	—	3.0	2.0	23 (−13–48)	26 (−8–50)
Severe nonproliferative or proliferative retinopathy§	—	—	—	2.4	1.1	47 (14–67)¶	47 (15–67)¶
Laser treatment§‖	—	—	—	2.3	0.9	56 (26–74)‡	51 (21–70)¶
Urinary albumin excretion (mg/24 hr)							
≥40	3.4	2.2	34 (2–56)¶	5.7	3.6	43 (21–58)‡	39 (21–52)‡
≥300	0.3	0.2	44 (−124–86)	1.4	0.6	56 (18–76)¶	54 (19–74)¶
Clinical neuropathy at 5 yr**	9.8	3.1	69 (24–87)¶	16.1	7.0	57 (29–73)‡	60 (38–74)‡

NEJM, 329:977-986, 1993

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

Glycemic control reduced retinopathy progression



Lancet, 352:837-853, 1998

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes

The ACCORD Study Group and ACCORD Eye Study Group*

Table 2. Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.*

Treatment	Progression of Diabetic Retinopathy	Adjusted Odds Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	no./total no. (%)			*no./total no. (%)*		
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.95 (0.80–1.13)	0.56
Intensive	104/1429 (7.3)			266/1629 (16.3)		
Standard	149/1427 (10.4)			273/1634 (16.7)		
Dyslipidemia therapy†		0.60 (0.42–0.87)	0.006		1.04 (0.83–1.32)	0.73
With fenofibrate	52/806 (6.5)			145/908 (16.0)		
With placebo	80/787 (10.2)			136/893 (15.2)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		1.27 (0.99–1.62)	0.06
Intensive	67/647 (10.4)			145/749 (19.4)		
Standard	54/616 (8.8)			113/713 (15.8)		

* Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye.
† Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.

NEJM, 363:233-244, 2010

BMJ

BMJ 2011;343:d4169 doi: 10.1136/bmj.d4169

RESEARCH

Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials

Rémy Boussageon *general practitioner and lecturer*[1], Theodora Bejan-Angoulvant *cardiologist, pharmacologist, and lecturer*[2 3 4], Mitra Saadatian-Elahi *epidemiologist*[2], Sandrine Lafont *resident in family medicine*[1], Claire Bergeonneau *resident in family medicine*[1 3], Behrouz Kassaï *pharmacologist and lecturer*[2 3 4 5], Sylvie Erpeldinger *general practitioner and lecturer*[1], James M Wright *anaesthesiologist, pharmacologist, and professor of anaesthesiology and pharmacology*[6], François Gueyffier *head of department and clinical investigation centre, cardiologist, and professor*[2 3 4 5], Catherine Cornu *endocrinologist, pharmacologist, and research physician in clinical investigation centre*[2 3 4 5]

Table 1| **Characteristics of studies included in meta-analysis**

Characteristic	UGDP 1975,[22] 1976[23]	UGDP 1982[24]	Kumamoto 1995[25]	Veteran Affairs[26]	UKPDS 1998 [9 27]	PROactive 2005[28]	Dargie et al 2007[29]	ACCORD 2008[7]	ADVANCE 2008[6]	VADT 2009[8]	HOME 2009[30]	Total
Jadad score	4	3	2	2	3	5	5	3	3	3	4	
No of participants	613	414	110	153	4209	5238	224	10 251	11 140	1791	390	34 533
No receiving intensive therapy	408	204	55	75	3071	2605	110	5128	5571	892	196	18 315
No receiving standard therapy	205	210	55	78	1138	2633	114	5123	5569	899	194	16 218
Men (%)	29	29	50	100	47	66	80	62	58	97	50	60*
Age (years)	52	52	49	60	53	62	64	62	66	60	61	61.8*

BMJ. 2011 Jul 26;343:d4169

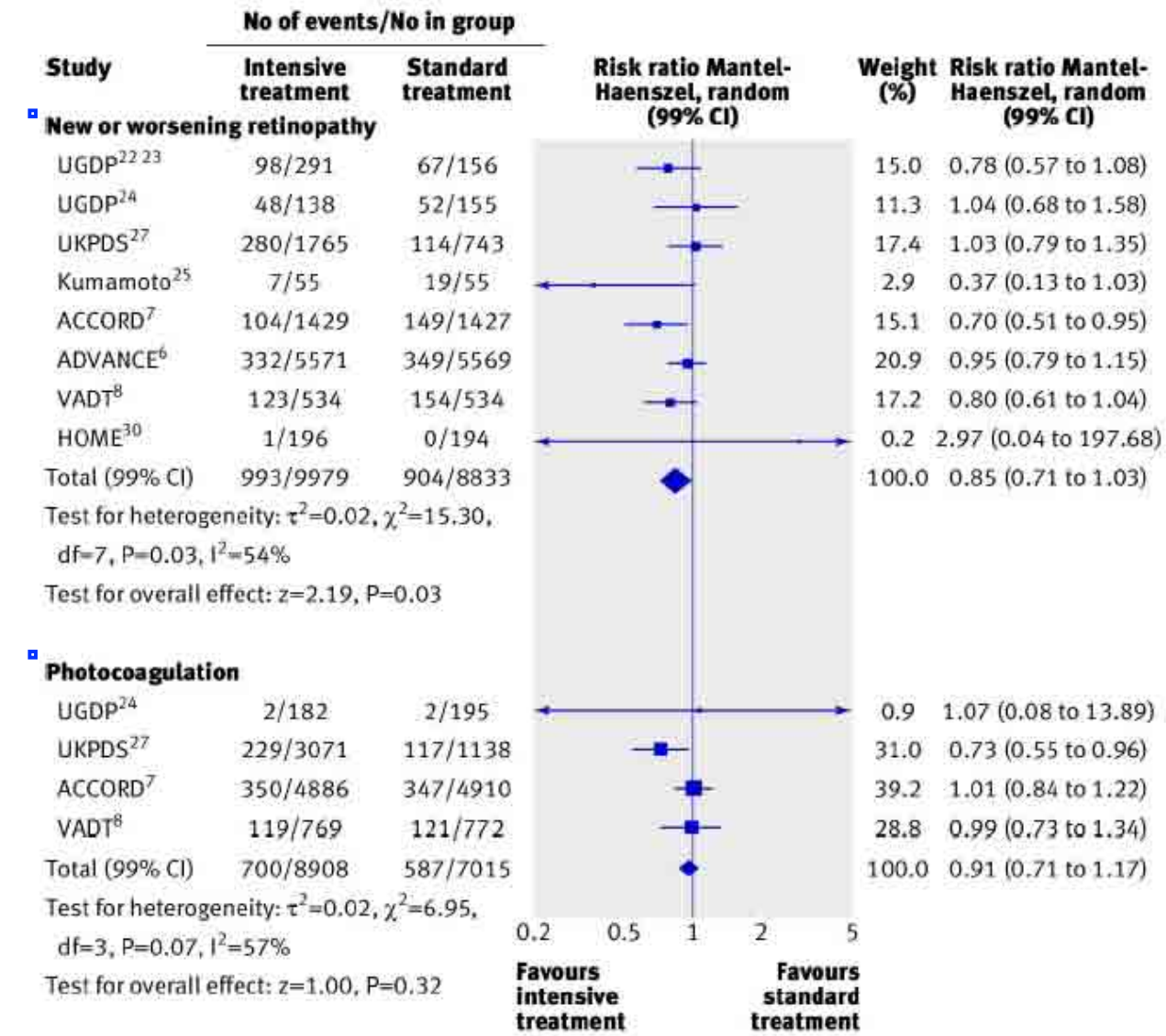
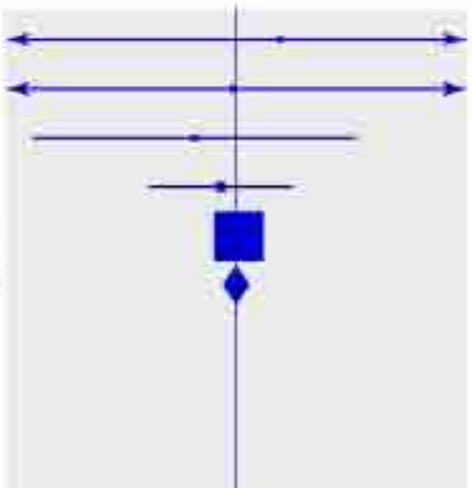


Fig 5 Forest plot for microvascular events: retinopathy and photocoagulation

BMJ. 2011 Jul 26;343:d4169



Study	No of events/No in group: Intensive treatment	Standard treatment	Risk ratio Mantel-Haenszel, fixed (99% CI)	Weight (%)	Risk ratio Mantel-Haenszel, fixed (99% CI)
Visual deterioration or blindness					
UGDP[22 23]	27/354	12/179		0.5	1.14 (0.48 to 2.69)
UGDP[24]	21/174	22/180		0.6	0.99 (0.47 to 2.06)
UKPDS[27]	90/3071	38/1138		1.6	0.88 (0.54 to 1.43)
ACCORD[7]	258/4651	273/4689		8.0	0.95 (0.77 to 1.18)
ADVANCE[6]	3033/5571	3015/5569		89.2	1.01 (0.96 to 1.05)
Total (99% CI)	3429/13 821	3360/11 755		100.0	1.00 (0.96 to 1.05)

Test for heterogeneity: χ^2=1.06, df=4, P=0.90, I^2=0%

Test for overall effect: z=0.01, P=0.99

BMJ. 2011 Jul 26;343:d4169

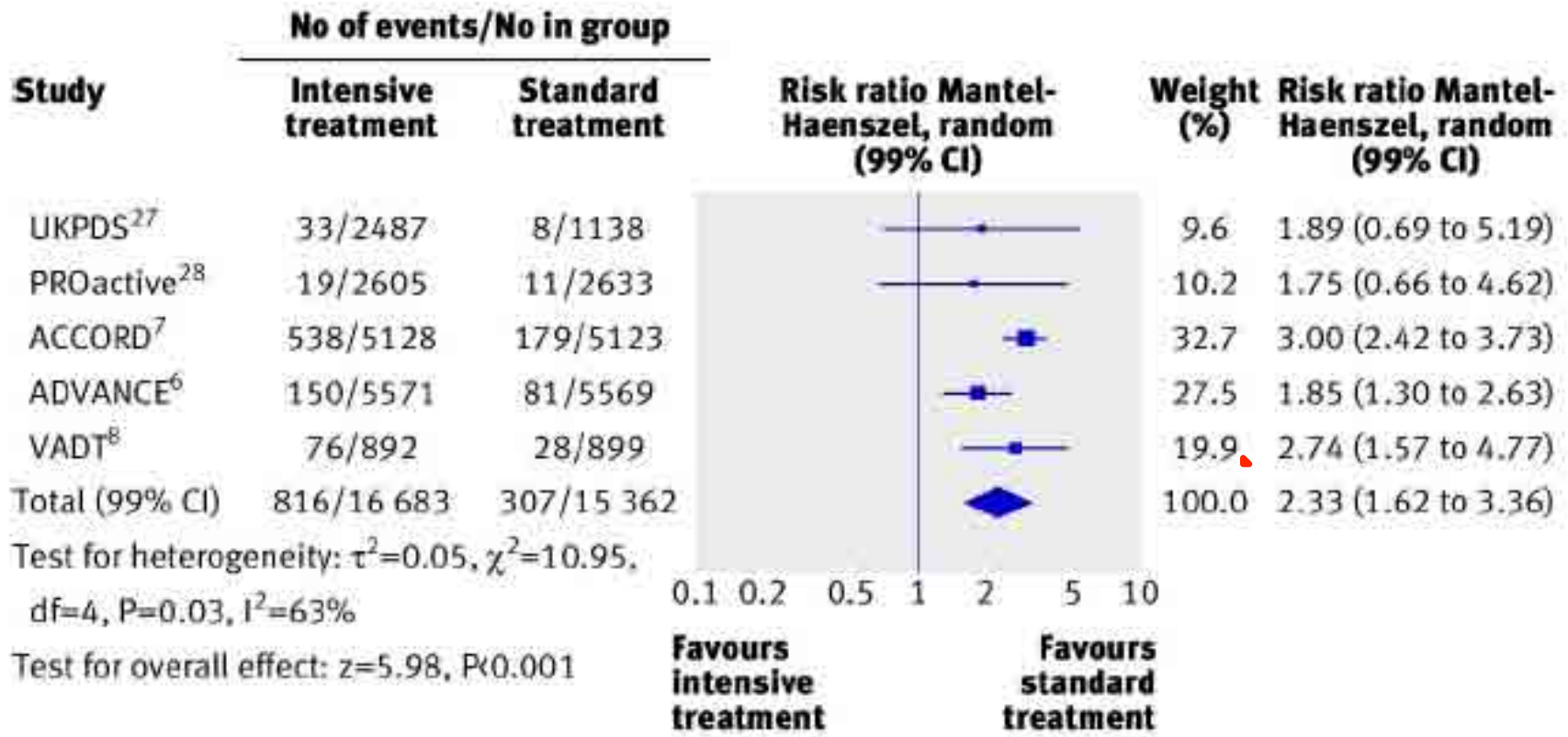


Fig 8 Forest plot for severe hypoglycaemia

BMJ. 2011 Jul 26;343:d4169

Risk of Developing Retinopathy in Diabetes Control and Complications Trial Type 1 Diabetic Patients With Good or Poor Metabolic Control

Table 1—*Development of retinopathy in type 1 diabetic patients from the DCCT primary cohort with good and poor metabolic control*

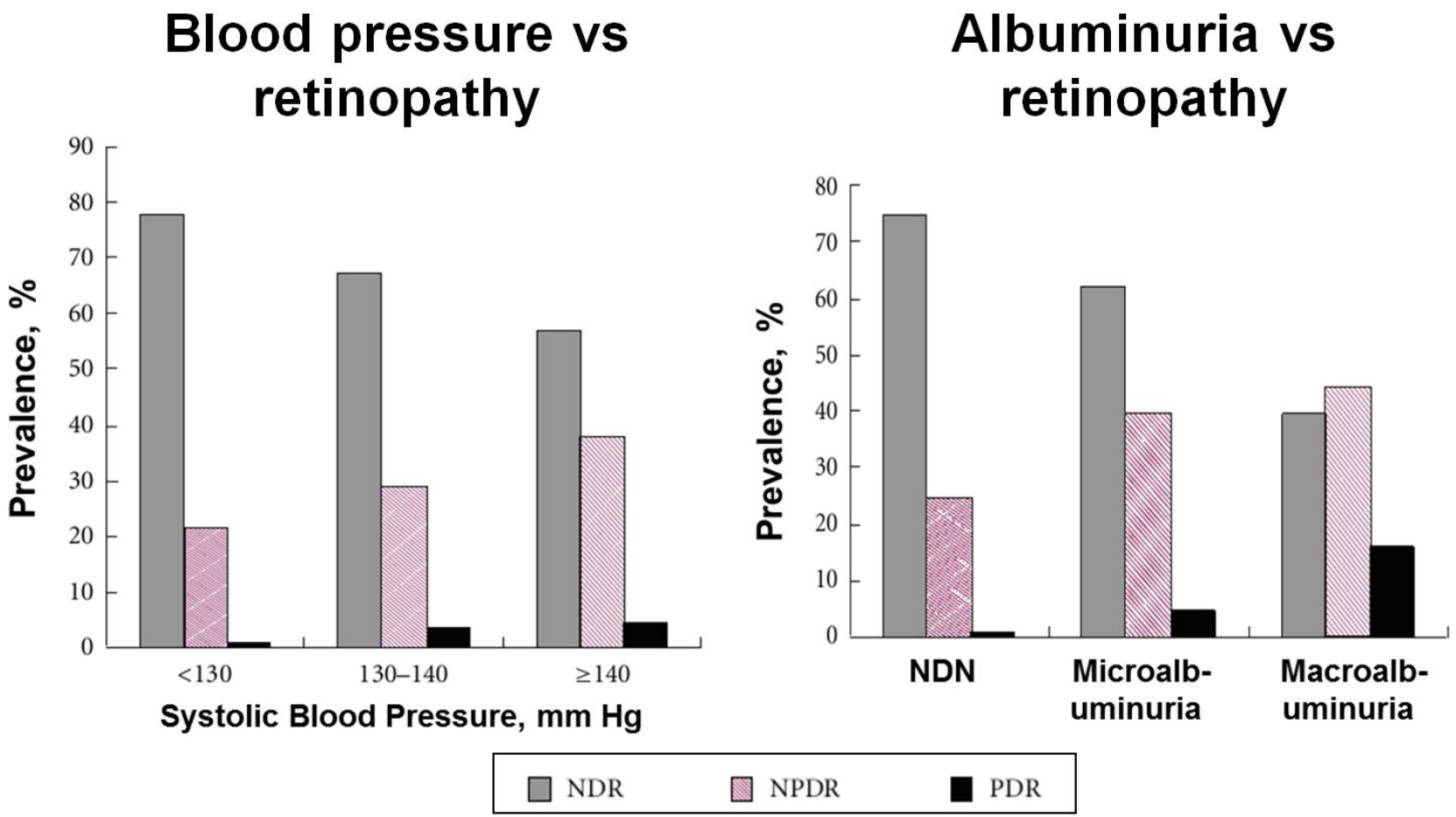
	Three-step retinopathy			
Metabolic control*	Absent	Change	Sustained	SNPDR
Good (n = 153)	138	15	0	0
HbA_{1c} ≤6.87%	90.2%	9.80%	0%	0%
Poor (n = 166)	71	38	54	3
HbA_{1c} ≥9.49%	42.8%	22.9%	32.5%	1.8%

Data are n or %. *OR 12.3 (95% CI 6.83–23.5).

Zhang et al, Diabetes care, 24:1275-1279, 2001

RD,
COMPENSO PRESSORIO
e SISTEMA RAA

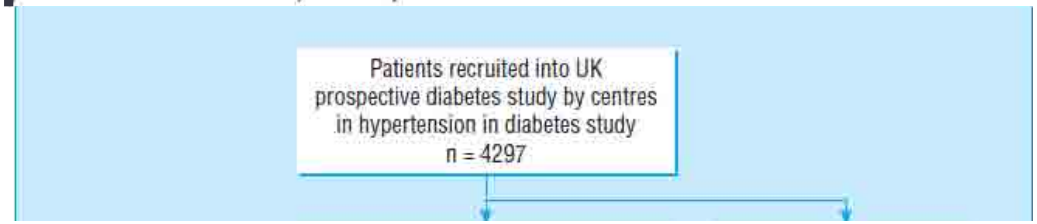
Risk Factors for Diabetic Retinopathy



He BB et al., Int J Endocrinol, 2012

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

UK Prospective Diabetes Study Group



Studio randomizzato controllato che confronta controllo pressorio più rigoroso vs controllo pressorio meno rigoroso

Follow up 8 anni

End point: eventi fatali e non fatali correlati al diabete, mortalità per tutte le cause

End points surrogati: microalbuminuria, progressione di RD

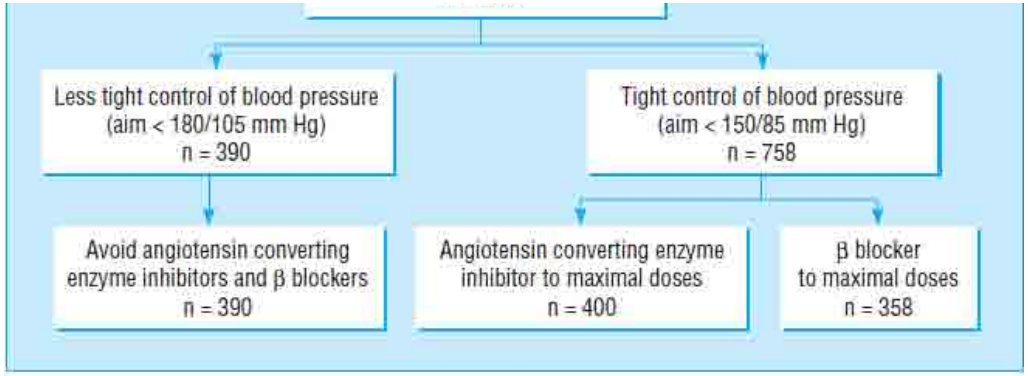
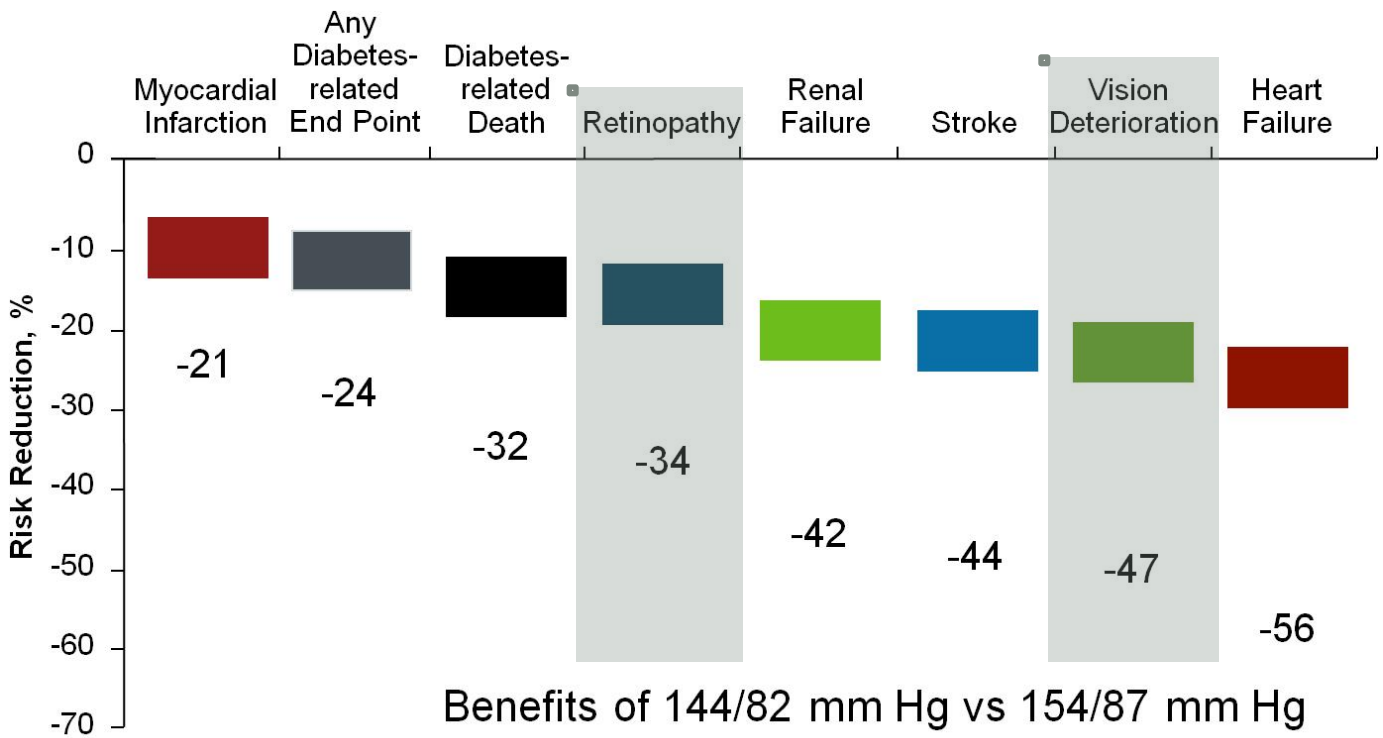


Fig 1 Selection and random allocation of patients to treatment in hypertension in diabetes study

BMJ, 317: 703-7013, 1998

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38

UK Prospective Diabetes Study Group



Captopril and atenolol were equally effective in reducing the risk of macrovascular end points. Similar proportions of patients in the two groups showed deterioration in retinopathy by two grades after nine years (31% in the captopril group and 37% in the atenolol group) and developed clinical grade albuminuria >300 mg/l (5% and 9%).

BMJ, 317: 703-7013, 1998

- Due trial randomizzati controllati in doppio cieco
- Partecipanti: pazienti diabetici tipo1 normotesi, normoalbuminurici
  - senza retinopatia (DIRECT-Prevent 1 trial)
  - con retinopatia (DIRECT-Protect 1)
- Assegnati a candesartan o a placebo
- Endpoints primari: incidenza e progressione di RD

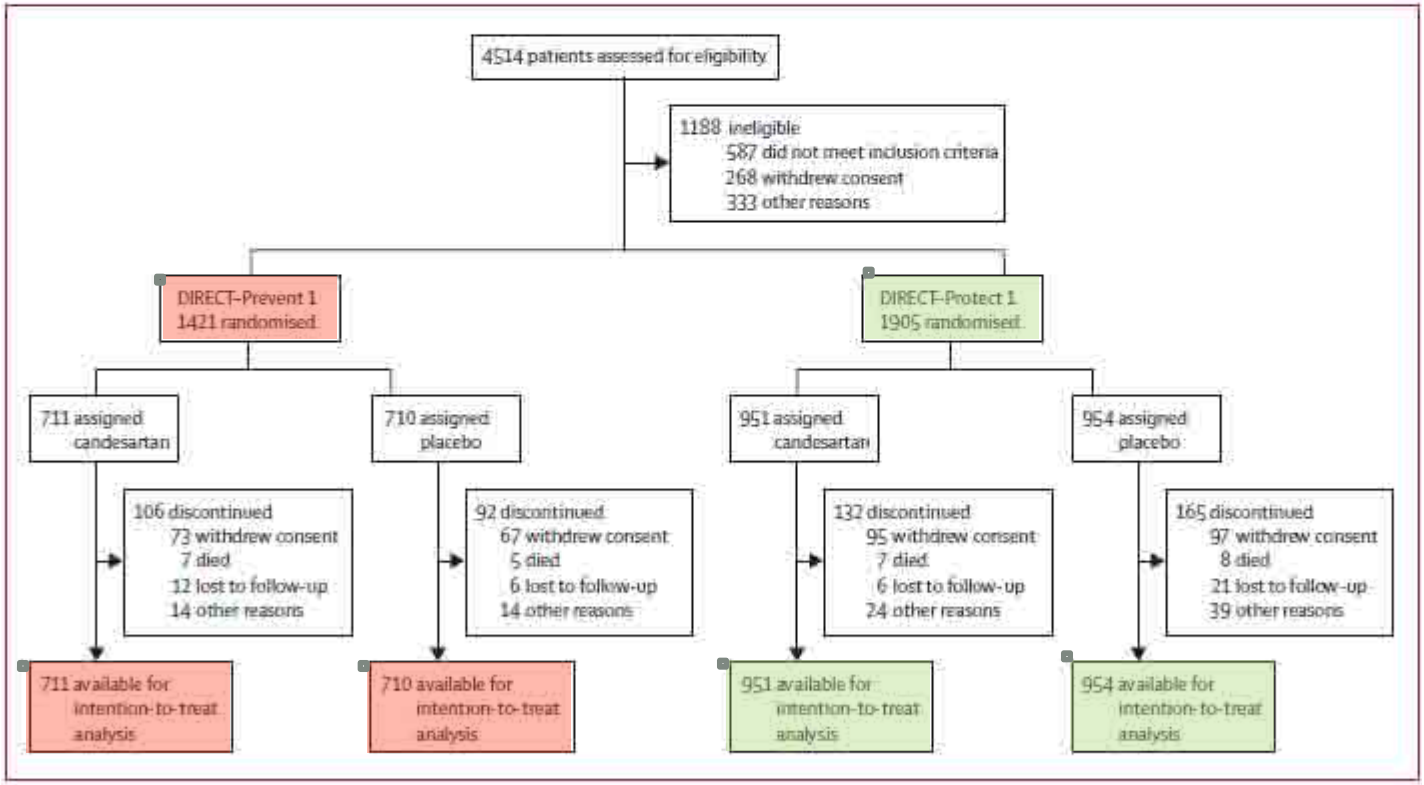


Figure 1: Trial profile

Chaturvedi et al., Lancet; 372: 1394-1402, 2008

Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

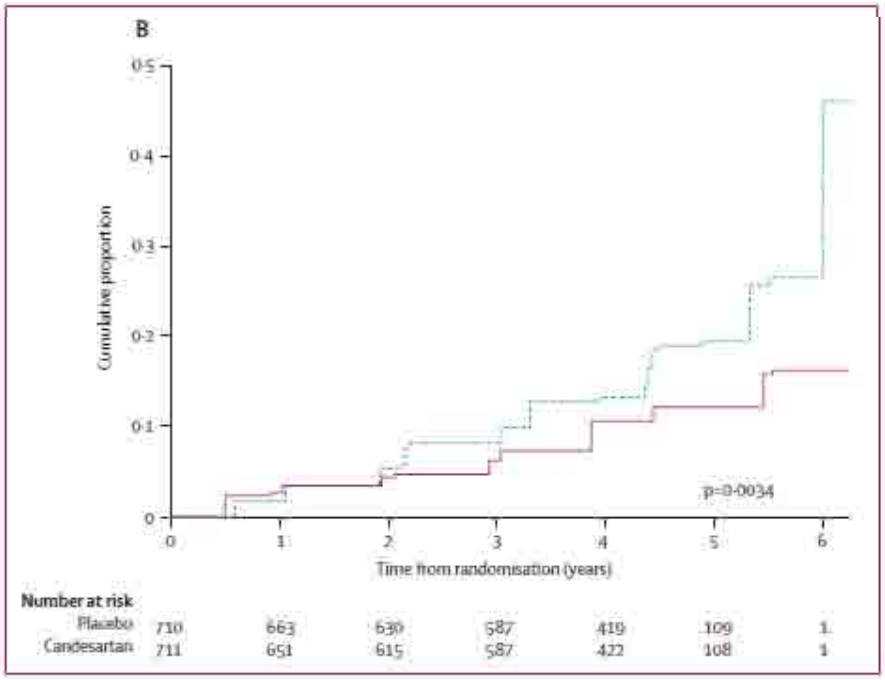


Figure 2: Cumulative proportion of patients with incidence of retinopathy by treatment allocation in Diabetic REtinopathy Candesartan Trials (DIRECT)-Prevent 1
(A) Incidence defined as at least a two-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. (B) Incidence defined as at a least three-step increase on the ETDRS scale.

We noted a 35% relative risk reduction in favour of candesartan in the post-hoc analysis (incidence: n=114 [16%] in placebo group, n=74 [10%] in candesartan group.
We noted some attenuation of the beneficial effect after we adjusted for baseline covariates, and further attenuation after we
adjusted for systolic blood pressure for the duration of the trial, although the effect of candesartan remained significant.

Chaturvedi et al., Lancet; 372: 1394-1402, 2008

Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

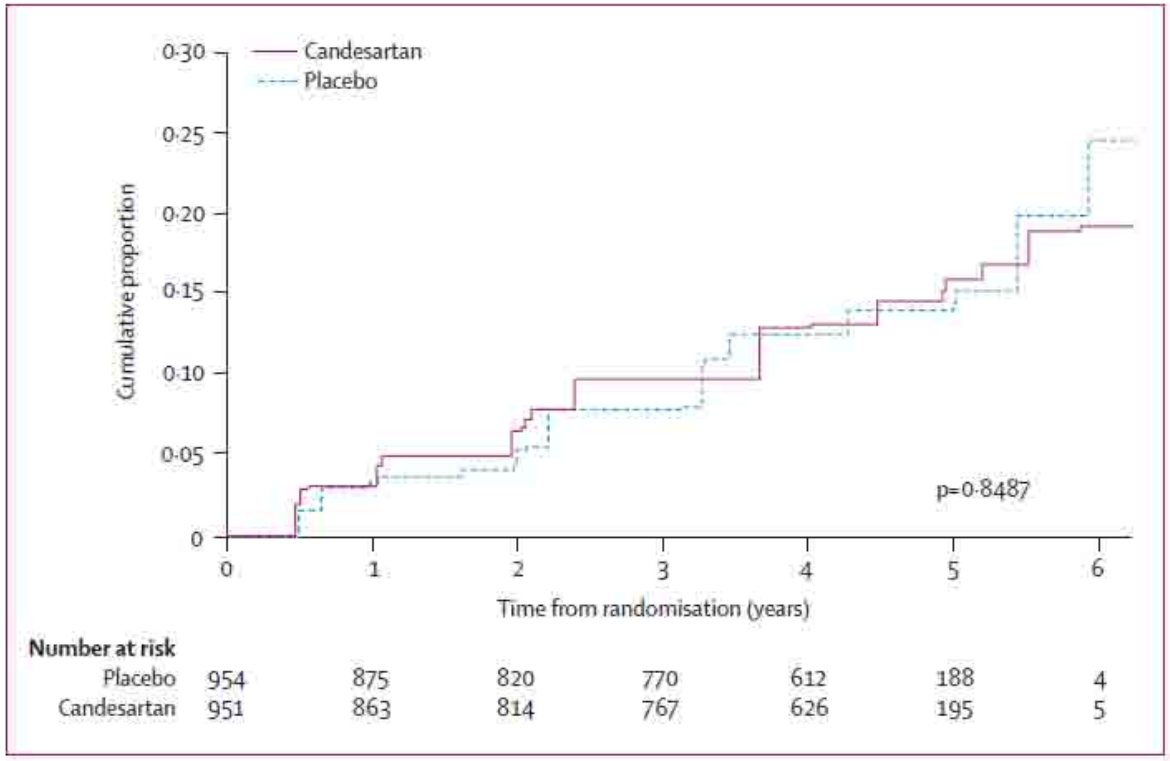


Figure 3: Cumulative proportion of patients with progression of retinopathy by treatment allocation in Diabetic REtinopathy Candesartan Trials (DIRECT)-Protect 1
Progression defined as at least a three-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

The initiation of retinopathy is thought to be due to the haemodynamic consequences of increased glucose concentrations, specifically increased resistance index and reduced retinal flow. These changes might be more responsive to renin-angiotensin system blockade than is more advanced retinopathy, which might be more a consequence of metabolic damage.

Chaturvedi et al., Lancet; 372: 1394-1402, 2008

- Trial randomizzato controllato in doppio cieco
- Partecipanti: pazienti diabetici tipo 2 normoalbuminurici, normotesi o ipertesi trattati (senza ACE-I o sartani)
- Con retinopatia non proliferante lieve o moderata-severa
- Assegnati a candesartan o a placebo
- Endpont primario: progressione di RD
- End point secondario: regressione di RD

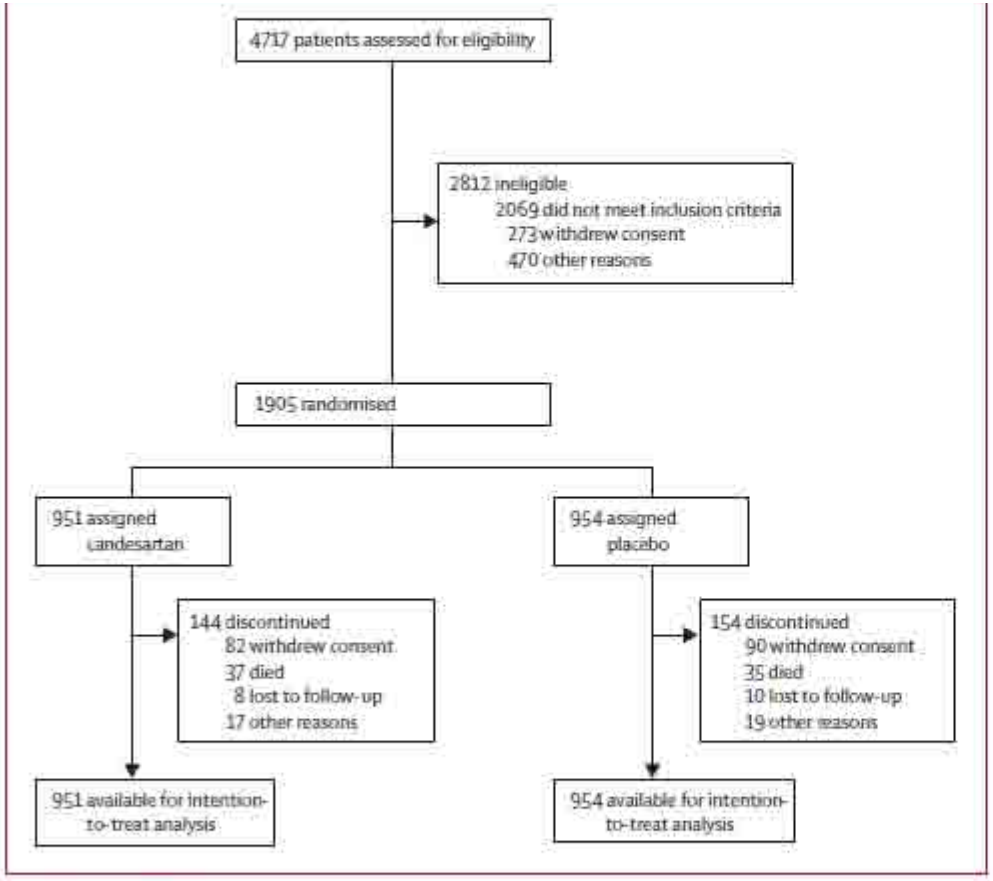


Figure 1: Trial profile

Sjolie AK et al., Lancet; 372: 1385-1393, 2008

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

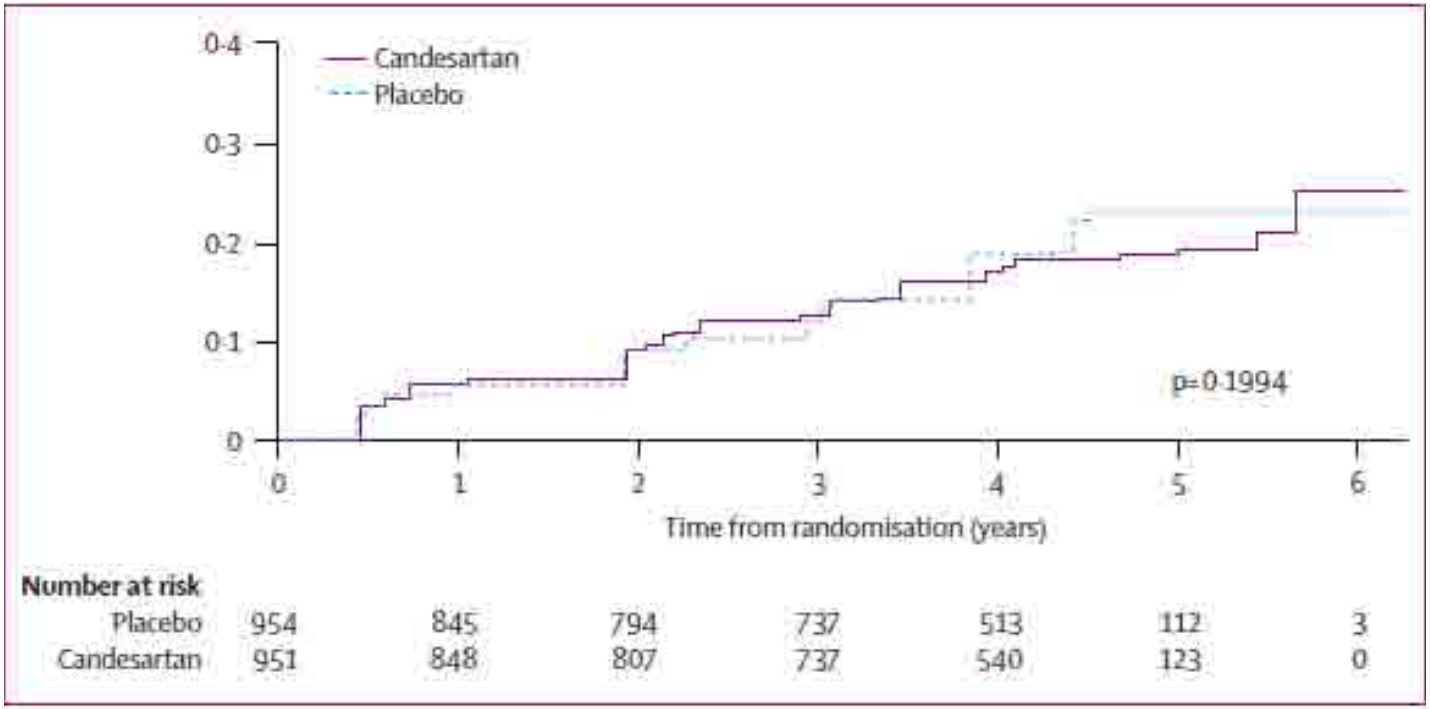


Figure 2: **Cumulative proportion of patients with progression of retinopathy by treatment allocation**

17% of 951 patients in the candesartan group and 19% of 954 in the placebo group had progression of retinopathy by three steps or more on the ETDRS scale (HR 0.87, 95% CI 0.70–1.08, p=0.20)

Sjolie AK et al., Lancet; 372: 1385-1393, 2008

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

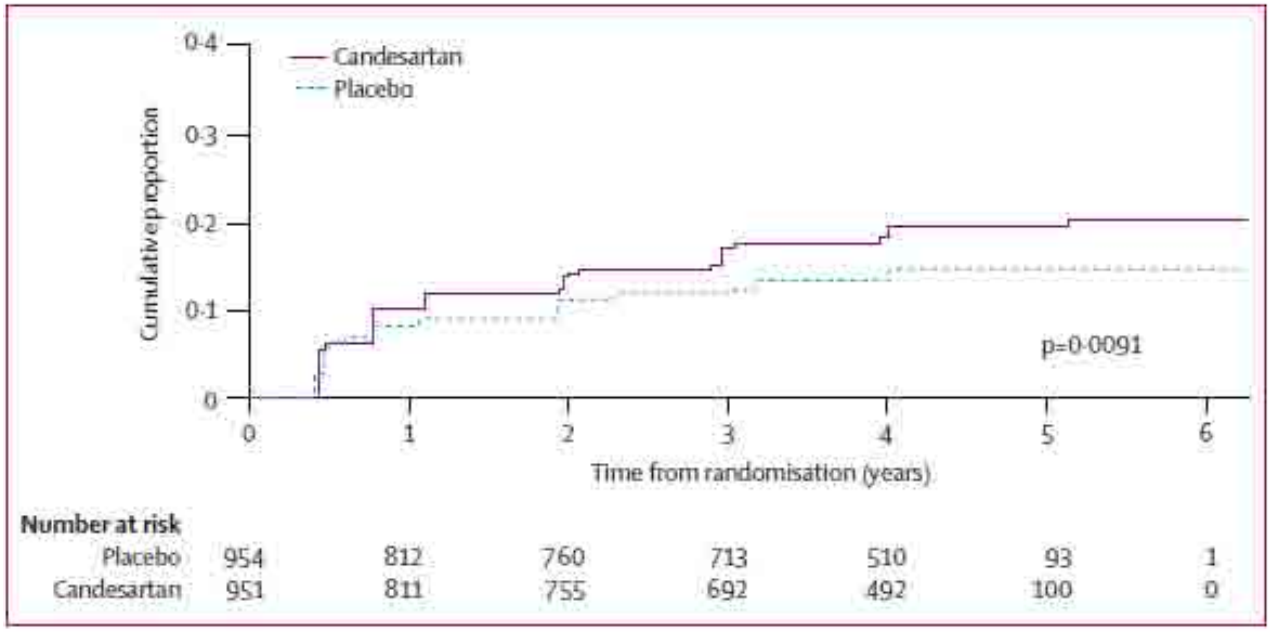


Figure 4: Cumulative proportion of patients with regression of retinopathy, by treatment group

19% participants in the candesartan group and 14% of controls had regression of retinopathy, which showed that candesartan was associated with a 34% increase in the relative chance of regression (p=0・009). The treatment effect was significant in patients with mild retinopathy, but not in those with moderate to moderately severe retinopathy.

Sjolie AK et al., Lancet; 372: 1385-1393, 2008

RD
E TRATTAMENTO ANTI-LIPIDICO

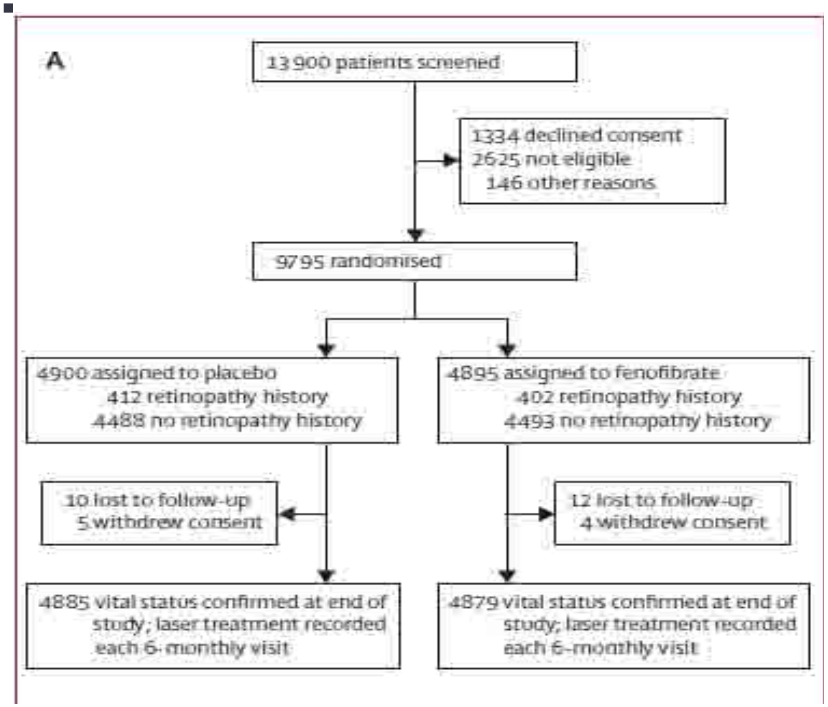
RD e STATINE

Study	Treatment	No	Follow-up (years)	Results
HPS	Simvastatin 40 mg	5.963	5	+8% laser treatment **(p=NS)**
CARDS	Atorvastatin 10 mg	2.832	4-4,5	-6% progression of retinopathy **(p=NS)** -13% photocoagulation **(p=NS)**
ASCOT-LLA	Atorvastatina 10 mg (+amlodipine)	2.532	3,3	+3% retinal thrombosis **(p=NS)**

Heart Protection Study Lancet 2003;361:2005-2016
Colhoun HM et al., Lancet. 2004;364:685-696
Sever PS et al., Diabetes Care 2005;28:1151-1157

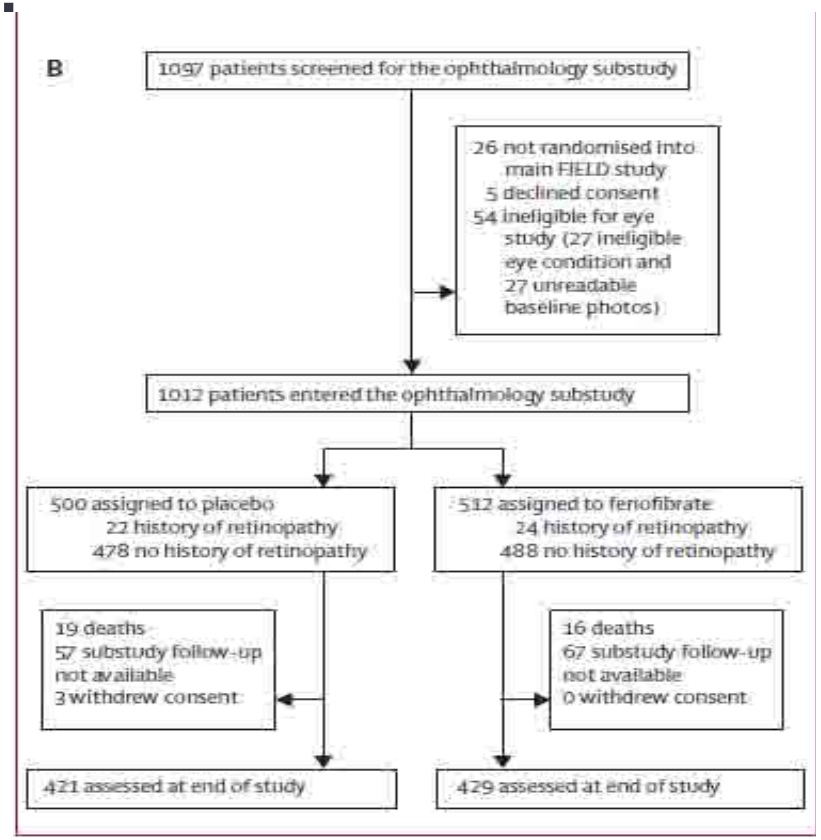
Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

MAIN PROTOCOL



Laser treatment recorded each six months visit

OPHTHALMOLOGY SUBSTUDY



Standardised retinal photography was done baseline, after 2 and 5 years

Lancet, 370:1687-1697, 2007

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

	Placebo (n=4900)		Fenofibrate (n=4895)	
	Number of patients (%)	Number of treatments	Number of patients (%)	Number of treatments
0	4662 (95%)	0	4731 (97%)	0
1	121 (2%)	121	85 (2%)	85
2	48 (1%)	96	38 (0·8%)	76
3	27 (0·6%)	81	17 (0·4%)	51
4	15 (0·3%)	60	9 (0·2%)	36
5	10 (0·2%)	50	8 (0·2%)	40
6–12	17 (0·3%)	127	7 (0·1%)	49
Cumulative total	238 (5%)	535	164 (3%)	337*

*p=0·0003 for difference in incidence density rates by treatment assignment (Poisson test).

Table 1: Number of laser treatment courses per patient during follow-up and cumulative totals by allocated treatment group

Lancet, 370:1687-1697, 2007

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

	Placebo group (n=500)	Fenofibrate group (n=512)	p value
Intercurrent events			
Laser treatment (one or more) for diabetic retinopathy	23 (4·6%)	5 (1·0%)	0·0004
Vitrectomy surgery	1 (0·2%)	2 (0·4%)	0·73
Cataract or cataract surgery	28 (5·6%)	37 (7·2%)	0·29
2-step progression of retinopathy (primary endpoint)			
All patients	57 (12·3%)	46 (9·6%)	0·19
No pre-existing retinopathy	43 (11·7%)	43 (11·4%)	0·87*
Pre-existing retinopathy	14 (14·6%)	3 (3·1%)	0·004*
Other outcomes diagnosed at scheduled eye visits (2 years, 5 years, study end)			
1-step progression of retinopathy grade	106 (22·9%)	104 (21·8%)	0·69
Occurrence of new retinopathy	45 (12·3%)	46 (12·1%)	0·96
Occurrence of new hard exudates	14 (3·1%)	16 (3·5%)	0·78
Any progression of hard exudates	2 (14·3%)	2 (13·3%)	0·99
2-line worsening in visual acuity (Snellen chart)	90 (29·1%)	97 (30·7%)	0·67
Occurrence of any macular oedema	10 (2·2%)	4 (0·8%)	0·09
Composite outcome of significant retinal pathology			
Any of 2-step progression of retinopathy grade, macular oedema, or laser treatment (either eye)	75 (16·1%)	53 (11·1%)	0·022

Data are n (%). *p value for interaction between treatment effects in those with and without pre-existing retinopathy=0·019.

Table 4: Main outcomes for the ophthalmology substudy

Lancet, 370:1687-1697, 2007

Management of Diabetic Retinopathy: Systematic Review

Glycemic control	**A, I**	**Lowering HbA_{1c} decreases development of new or progression of existing diabetic retinopathy HbA_{1c} < 7% is ideal**
Blood pressure control	A, I	Blood pressure treatment reduces development of new or progression of existing diabetic retinopathy Systolic < 130 mm Hg is ideal ACE inhibitor/ARB benefit
Lipid-lowering therapy	A, II	LDL-C lowering reduces macrovascular complications, may benefit diabetic macular edema Fibrate benefit?

Mohamed Q, et al. JAMA, 298: 902-916, 2007

What else can we do?

RAZIONALE PER PROGRAMMA DI SCREENING

La RD è una grave problema di salute pubblica

La RD ha una lunga fase asintomatica

Il programma di screening tramite FOO
è sicuro, efficace e cost-effective

Screen!

Retinopatia diabetica proliferante e edema maculare....

Fotocoagulazione laser

Farmaci intra-vitreali

In conclusione:

1. RD rimane un'importante causa di peggioramento dell'acuità visiva e di cecità
2. Il controllo glicemico è efficace, soprattutto nella prevenzione primaria della RD e nella riduzione di progressione degli stadi molto iniziali
3. Il controllo pressorio è probabilmente importante in tutti gli stadi di RD
4. L'uso di farmaci bloccanti il sistema RAA può essere efficace negli stadi di RD non proliferante lieve
5. L'uso di fenofibrato può avere un ruolo nell'arrestare la progressione della RD negli stadi non proliferanti moderati-severi
6. Lo screening della retinopatia diabetica è indispensabile!
7. Negli stadi di RD più avanzati (PRD e DME): laser-terapia e farmaci intra-vitreali

Grazie per l’attenzione!